

Remarks

I. Status of the Application and Claims

As originally filed, the present application had a total of 4 claims. These were cancelled in a Preliminary Amendment and new claims 5-24 were added. No claims were cancelled, added or otherwise amended herein.

II. Claim Objections

On page 2 of the Office Action, the Examiner maintains an objection to claims because they contain non-elected species and the Examiner has concluded that the "Markush" claim, *i.e.*, claim 5, is not patentable. As discussed in the response filed on July 21, 2008, when this occurs the procedure, as understood by Applicants, is to continue Examination on the Markush claims along with claims that include the elected species and to withdraw claims that only include nonelected species. Since there are no claims in the application directed solely to non-elected species, Applicants do not believe that any claims need to be withdrawn or that amendments to eliminate subject matter from dependent claims need to be made at present.

The Rejections

On pages 2-3 of the Office Action, the Examiner maintains a rejection of all pending claims as being obvious over Dormoy, *et al.* (*Synthesis*, pg. 81-86 (1996)), in view of Carlsen, *et al.*, (*J. Org. Chem.* 46:3936-3938 (1981)) and Riley, *et al.* (*J. Chem. Soc., Chem. Commun.*, 1530-1532 (1983)) and further in view of Narukawa, *et al.* (*Tetrahedron* 53:539-556 (1997)). The Examiner has alleged that Dormoy teaches the conversion of hydroxyprolines to ketoprolines using a ruthenium catalyst in a biphasic organic solvent system. Carlsen and Riley were both cited as teaching ruthenium catalyzed oxidations in solvent systems containing water and Narukawa was cited as teaching that t-boc protected oxo-proline compounds are not very soluble in water.

Applicants respectfully traverse this rejection.

As discussed in Applicants' previous response, ketoproline is unstable in the sense that, after oxidative synthesis, it has a tendency to undergo further reaction. It must therefore be stabilized in some manner to avoid the accumulation of unwanted side products. Applicants have accomplished this stabilization by inducing the precipitation of the ketoproline at the same time that oxidizing agent is being added to the reaction mix. It is Applicants' position that none of the references that have been cited disclose this either alone or in combination. Three of the references, Dormoy, Carlsen and Narukawa,¹ use a two phase reaction system and purify the products produced by extraction. Riley uses a one phase system in some reactions but does not appear to consider the production of ketoproline and does not stabilize the products made by precipitation.

In the present Office Action, the Examiner comments on the arguments made by Applicants in responding to the rejection of claims under 35 USC §103. Below, Applicants respond to comment.

Response to First Comment

The Examiner states that Applicants' argument concerning the precipitation of ketoproline at the time that oxidizing agent is added is not persuasive because it has been established that the order in which ingredients are added to a mixture does not make an invention patentable.

In response, Applicants submit that the present claims do not merely require combining ingredients but rather performing a reaction step, inducing precipitation, that is essential to stabilizing the product made. This may be contrasted with the Dormoy, Carlsen and Narukawa references where stabilization is apparently achieved by separating reaction components in a two phase system and with the Riley reference where it is not clear that any steps were taken to stabilize products at all. Inducing precipitation, *e.g.*, by adding seed crystals, is not something that is done or suggested in any cited reference and clearly involves more than just changing the order that ingredients are added to a mixture.

¹ Applicants believe the only ketoproline that is disclosed in Narukawa is compound 15 on page 549 and assume that the Examiner is referring to this compound in rejecting claims.

In addition, Applicants submit that it is not just the time at which oxidizing agent is added that is important to Applicants' method but rather the relationship between the time that the precipitation of reaction product is induced and the time that oxidizing agent is added. The addition and precipitation are done concurrently to minimize the further reaction of the ketoprolines produced. There does not appear to be any incentive to do this in the Dormoy, Carlsen and Narukawa references because stabilization has already been achieved by virtue of the use of a two phase system. There is no incentive to do this with Riley since there is no indication that any of the products described therein are unstable.

Response to Second Comment

The Examiner alleges that Applicants' argument that Riley does not include ketoprolines among the products described therein is not persuasive because the "combined references suggest to one of ordinary skill to make the modifications necessary to practice the instant invention with a reasonable expectation of success."

In response, Applicants submit that there is no indication that the compounds studied by Riley have the same problem with stability as the ketoprolines. As far as Applicants can tell, Riley did not perform any stabilization steps and this certainly seems to suggest that stability was not a problem. In the absence of evidence to the contrary, there would be no reason for one carrying out the process of Riley to adopt a two phase reaction system (*e.g.*, the system of Dormoy, Carlsen or Narukawa) or to precipitate the reaction product concurrently with the addition of reactant. Similarly, there would be no incentive for one carrying out the process of Dormoy, Carlsen or Narukawa to produce ketoprolines in the one phase systems described in Riley since the stabilization of the reaction product would be lost.

Response to Third Comment

The Examiner alleges that even if Narukawa does not expressly teach that ketoprolines are poorly soluble in water, poor solubility can be inferred from the teachings on page 549 (presumably in connection with compound 15).

In response, Applicants submit that it is not entirely clear what the Examiner is relying on to infer poor water solubility. The reference does indicate that compound 15 can be

extracted using ethyl acetate. However, an extraction will be influenced by the polarity of the solvents used and it is therefore not clear how much can be ascertained concerning the aqueous solubility of ketoproline from the disclosure. One thing that is very clear is that compound 15 was extracted from a two phase system and not precipitated. Moreover, since the compound was already stabilized in the reaction by using a two phase system, there is no inference that precipitations might improve the method.

Conclusion

In light of the discussion above, Applicants respectfully submit that the Examiner's rejections have been overcome. It is therefore requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (240)683-6165.

Respectfully submitted,
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